REMARKS

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Status of the Claims

Claims 1-12, 17-21, 27-30, 37-49, 54-58, 63-67, 91-95, and 100-104, 111, 128-130, 138, 151, 164, and 177 have been canceled by previous amendment without prejudice or disclaimer. Accordingly, claims 13-16, 22-26, 31-36, 50-53, 59-62, 68-73, 87-90, 96-99, 105-110, and 112-127, 131-137, 139-150, 152-163, 165-176, and 178-195 are pending and at issue.

Obviousness-type Double Patenting and Common Ownership Rejections

Claims 13-16, 22-26, 31-36, 50-53, 59-62, 68-73, 87-90, 96-99, 105-110, and 112-127, 131-137, 139-150, 152-163, 165-176, and 178-195 stand rejected under the judicially created doctrine of obviousness-type double patenting over various claims of U.S. Patent Nos. 6,071,538, 5,714,167, 6,348,207 and 6,221,367. Applicants respectfully disagree with the rejection. Upon the finding of allowable subject matter, applicants will consider filing a terminal disclaimer.

Rejections Under 35 U.S.C. § 103(a)

Claims 13-16, 22-26, 31-36, 50-53, 59-62, 68-73, 87-90, 96-99, 105-110, and 112-127, 131-137, 139-150, 152-163, 165-176, and 178-195 stand rejected as obvious over Makino, et al. (U.S. Patent No. 4,746,675; hereafter "Makino") in view of Morishita, et al. (U.S. Patent No. 4,873,087; hereafter "Morishita").

Applicants respectfully traverse this rejection and request reconsideration.

"To establish a *prima facie* case of obviousness, ... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of \\W:\01946\100a483us8\00803161.DOC \\ \Bar{A} \Bar{A

ordinary skill in the art, to modify the reference or to combine reference teachings." M.P.E.P. §2143; In re Kahn, 441 F.3d 977, 986 (Fed. Cir. 2006) (To establish a prima facie case of obviousness, the Examiner must "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious") (quoting In re Rouffet, 149 F.3d 1350, 1357-59 (Fed. Cir. 1998)), reh'g en banc denied; Teleflex, Inc. v. KSR Int'l Co., 119 Fed. Appx. 282, 285; 2005 U.S. App. LEXIS 176, *7 (unpub.) (Fed. Cir. 2005), cert. granted.

Here, the Examiner has not satisfactorily explained the reasons one of ordinary skill in the art would have been motivated to select and combine Makino and Morishita. The Examiner merely states what each reference teaches, but does not offer any explanation as to why a person would have been motivated to combine the references:

[I]t would have been obvious to one of ordinary skill in the art at the time of the invention was made to use the compositions of Makino et al. or Morishita et al. for administration of biologically active agent[s] subcutaneously since Makino et al teach oral or injection route of administration and [a] penetration enhancer, Morishita et al. teaches administration through rectum or vagina, which are lined by mucosal membranes.

Applicants respectfully submit that the Examiner has not satisfied the Examiner's burden to establish motivation to combine simply based on Makino's purported teaching of a penetration enhancer and oral or injection routes of administration, and Morishita's teaching of compositions

¹ Applicants note that Makino is directed to external pharmaceutical compositions, not injections. While Makino refers to administering active agents that, when administered via injection, exhibit undesirable physiological action, it does not disclose injections containing an active agent <u>and</u> a penetration enhancer (see Makino, col. 3, lines 38-46). Accordingly, the Examiner's statement that Makino teaches administration via injection is misleading to the extent that it suggests that the penetrations enhancers of Makino can be used to facilitate injectable formulations (compare claims 13 - 20, 22-26, 31-36 and 112-137 of the present invention, which relate to compositions containing an active agent and a perturbant for subcutaneous administration). Makino actually teaches away from the injection of active agents with penetration enhancers.

using different compounds to enhance absorption through the colon, rectum or vagina. In the absence of further reasoning by the Examiner to establish a motivation to combine the references, Applicants submit that the references are not properly combined (Or was Makino properly cited in view of Morishita) and that a *prima facie* case of obviousness has not been established.

Even assuming, *arguendo*, that it was appropriate for the Examiner to combine (or cite Makino in view of Morishita), the references, taken alone or combined, do not teach every limitation of the pending claims and, thus, the obviousness rejection is improper. The claims call for a perturbant selected from either a carboxylic acid or acylated amino acid of specified formulae; neither reference teaches such a perturbant. The Examiner admits that Makino does not teach a carboxylic acid (Office Action of April 19, 2006, at pg. 5, line 11). The Examiner contends, however, that Makino discloses a pyroglutamic acid derivative penetration enhancer that reads on the claimed acylated amino acids. Makino's penetration enhancer has the following formula:

wherein R_1 and R_2 are independently hydrogen, C_1 - C_{25} alkyl, C_2 - C_{25} alkenyl, C_1 - C_{24} alkyl carbonyl or a C_2 - C_{24} alkenyl carbonyl. The presently recited acylated amino acid has the following formula:

$$Ar \xrightarrow{C} C \xrightarrow{C} N(R^{16}) \xrightarrow{R^{15}} C \xrightarrow{N} OH$$

wherein R¹⁵ is, *inter alia*, an alkyl, alkenyl, or aryl group, R¹⁶ is, for example, H, or an alkyl or alkenyl group, and n is 1-5.

Contrary to the Examiner's contention, Makino's penetration enhancer does not read on the claimed acylated amino acid since Makino does not disclose a compound with a terminal COOH group and an uninterrupted, terminal aryl group.

The Examiner further contends that Morishita discloses an N-acyl amino acid absorption promoter *prepared from* a carboxylic acid and an amino acid. According to the Examiner, the carboxylic acids and amino acids used for preparing the absorption promoter include those described in the instant specification.

Notwithstanding the Examiner's contention, the accuracy of which need not be argued in this filing, Morishita clearly does not teach or suggest the presently claimed *perturbants* as final products. The compounds disclosed in columns 4 and 6 of Morishita *are merely intermediates* used to produce Morishita's absorption promoter shown in formula I. According to the Manual of Patent Examining Procedure:

"If the prior art merely discloses compounds as intermediates in the production of a final product, one of ordinary skill in the art <u>would not have</u> <u>been motivated</u> to stop the reference synthesis and investigate the intermediate compounds with an expectation of arriving at claimed compounds which have different uses."

(MPEP § 2144.09, *citing*, *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1994), emphasis added). Therefore, it would not have been obvious to one of ordinary skill in the art to use the *intermediates* of Morishita as perturbants, as claimed.

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Furthermore, Morishita neither teaches nor suggests the use of the claimed perturbants as an absorption promoter, i.e., the final product of Morishita, shown in Formula I, does not read upon the presently claimed perturbants.

Accordingly, neither Makino nor Morishita, either alone or in combination, teach or suggest the claimed carboxylic acids or acylated amino acid perturbants and, thus, the Examiner has not provided a valid *prima facie* case of obviousness.

Consequently, the Applicants respectfully request withdrawal of all rejections and the allowance of all pending claims.

Dated: July 19, 2006

Respectfully submitted,

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